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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/594,401

09/26/2006

Kenichi Koyakumaru

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LEYDIG VOIT & MAYER, LTD
TWO PRUDENTIAL PLAZA, SUITE 4900
180 NORTH STETSON AVENUE
CHICAGO, IL 60601-6731

EXAMINER

CLARK, SARA E

ART UNIT

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/594,401	Applicant(s) KOYAKUMARU, KENICHI	
	Examiner SARA E. CLARK	Art Unit 4121	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-9 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-9 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____. |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>12/20/2006</u> . | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

This is a national stage (35 U.S.C. 371) application of PCT/JP05/06819, filed 3/31/2005, which claims benefit of priority to Japanese application 2004-108443, filed 3/31/2004. Claims 1-9 are pending.

Priority

1. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. Claims 1-9 are entitled to an effective filing date of 3/31/2005.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on 12/20/2006 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

Specification

3. The disclosure is objected to because of the following informalities: the side chain hydroxyl group is identified throughout as the 21-hydroxyl group, although structural formulae I-VII show the hydroxyl group bonded to carbon 22. (see Moss, IUPAC Nomenclature of Steroids, p. 3). To avoid confusion, this Office Action refers to the side chain hydroxyl group as the 21-hydroxyl group, consistent with the specification and claims. However, appropriate correction is required.

Claim Objections

4. Claims 1-9 are objected to because of the following informalities: the side chain hydroxyl group is identified as the 21-hydroxyl group, although structural formulae I-VII show the hydroxyl group bonded to carbon 22 (see Moss, IUPAC Nomenclature of Steroids, p. 3). To avoid confusion, this Office Action refers to the side chain hydroxyl group as the 21-hydroxyl group, consistent with the specification and claims. However, appropriate correction is required.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1, 2, and 5 rejected under 35 U.S.C. 102(b) as being anticipated by Nakazawa et al. (US PG Pub. 2003/0181742, published 9/25/2003, supplied by Applicant on the IDS dated 12/20/2006), as evidenced by Koyakumar et al. (US PG Pub. 2007/0197490, published 8/23/2007).

Nakazawa et al. teach a method of producing 5 α -pregnane derivatives as intermediates useful in squalamine synthesis, starting with (20S)-7 α ,21-dihydroxy-20-methyl-pregna-1,4-dien-3-one as a reactant (para. 20, “the diene”) and resulting in (20S)-7 α ,21-dihydroxy-20-methyl-5 α -pregna-3-one as a product (para. 21, “the ketone”).

Formula II-1 of Nakazawa et al. ((20S)-7 α ,21-dihydroxy-20-methyl-5 α -pregna-3-one, the unprotected ketone, para. 21) is identical to formulae I and III, which are coextensive with one another, where R1, R2, R11, and R12 are each independently a hydrogen atom, as recited in claims 1-5; and identical to formula VII as recited in claims 6-9.

Formula III-1 of Nakazawa et al. ((20S)-7 α ,21-di-(O-protecting group)-20-methyl-5 α -pregna-3-one, the protected ketone, para. 22) is identical to formulae I and III, which are coextensive with one another, as recited in claims 1-5, where R1, R11, R2, and R12 are each a hydroxyl-protecting group; and identical to formula IV and VI, which are coextensive with one another, as recited in claims 6-9, where R22 and R32 are each a C7-hydroxyl-protecting group.

The method of Nakazawa et al. teaches the steps of

(a) reducing the diene double bonds at C1-C2 and C4-C5 to single bonds with lithium in the presence of ammonia or an amine (known as the Birch reduction, paras. 12, 13, 50), in the presence of a proton donor such as ethanol (paras. 53, 72), to obtain the ketone of Formula II-1; and

(b) protecting the C7 and C21 hydroxyl groups of the ketone with tert-butyl-dimethylsilyl protecting groups (paras. 14, 15, 42), to obtain the ketone of Formula III-1.

Nakazawa et al. do not explicitly teach the ene-one of formula II, recited in claims 1-5 ((20S)-7 α ,21-dihydroxy-20-methyl-pregna-1-en-3-one), in which neither, one, or both hydroxyl groups are protected; or formula V, recited in claims 6-9 ((20S)-7 α -hydroxy-21-(O-protecting group)-20-methyl-pregna-1-en-3-one), the ene-one where the

C21 hydroxyl group is protected and the C7 hydroxyl group is either free or protected. Therefore, Nakazawa et al. do not explicitly teach a mixture of formulae I and II (the reactant mixture recited in claims 1-5) or a mixture of formulae IV and V (the reactant mixture recited in claims 6-9).

However, the ene-one of formula II is inherently formed during the course of the reduction step taught by Nakazawa et al. Specifically, Nakazawa et al. teach the use of an alkali or alkaline earth metal, including lithium (para. 50); ammonia or an amine (paras. 48-49); an alcohol (para. 53); at a temperature ranging from -80 to 30° C (para. 54). These are substantially the same reaction conditions employed in the disclosure of 10/594,163: an alkali or alkaline earth metal, including lithium, the amount of which is not particularly limited (p. 14, lines 26-32); ammonia or an amine (p. 15, lines 17-30); an alcohol (p. 15, line 31 to p. 16, line 26); at a temperature ranging from -50 to 20° C (p. 15, lines 11-13). Under these conditions, US PG Pub. 2007/0197490 discloses that “it was newly found that, in this reaction, the reduction reaction of the carbon-carbon double bond at the 4,5-positions of a (20S)-7 α ,21-dihydroxy-20-methylpregna-1,4-dien-3-one derivative proceeds significantly faster than the reduction reaction of the carbon-carbon double bond at the 1,2-positions” (p. 4, lines 4-9).

Therefore, since the reduction of the C4-C5 double bond proceeds faster than the reduction of the C1-C2 double bond under the conditions taught by Nakazawa et al., the process of Nakazawa et al. inherently forms an intermediate mixture of the ketone and 1-ene-one (formulae I and II as recited in claims 1-5, or IV and V as recited in claims 6-9) until the reduction of the ene-one has gone to completion. Under the

conditions taught by Nakazawa et al. and the disclosure of 10/594,163, this two-part reduction occurs as an intrinsic part of the process regardless of whether it was known or explicitly taught. The result of Nakazawa et al. is a selectively reduced ketone product, in which the diene double bonds are reduced but the carbonyl oxygen is not, which is also the aim of the present invention. In summary, Nakazawa et al. explicitly teach formulae I, III, IV, VI, and VII, a reduction step, and a protection step; and inherently teach the 1-ene-one of formula II, and a reactant mixture of formulae I and II, as recited in claims 1, 2, and 5.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. Claims 1-4, and 6-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nakazawa et al. (cited above) in view of Moriarty et al. (Tetrahed. Let. 35 (44) 8103-6, 1994) as evidenced by Koyakumar et al. (US PG Pub. 2007/0197490, published 8/23/2007).

As discussed in paragraph 6 above, Nakazawa et al. teach formulae I through IV, VI, and VII; a reduction step in a reactant mixture of formulae I and II; and a protection step.

However, Nakazawa et al. do not teach the 1-ene-one of formula V ((20S)-7 α -hydroxy-21-(O-protecting group)-20-methyl-pregna-1-en-3-one, where the C21 hydroxyl group is protected and the C7 hydroxyl group is either free or protected), because it is not inherently formed during the process; therefore, nor is the reactant mixture of formulae IV and V taught, as recited in claims 6-9. This is because the method of Nakazawa et al. teaches the reduction step followed by the protection step, rather than hydroxyl group protection prior to the reduction step, as recited in the instant claims.

Moriarty et al. teach hydroxyl-group protection prior to the reduction step as part of a multi-step synthesis of squalamine, in which the similarly reactive side chain hydroxyl group at C24 is protected with a tert-butyldimethylsilyl protecting group (step iv, yielding compound 4, pp. 8103-4), before the ene-one compound is subjected to the Birch reduction, using lithium in ammonia and ethanol (step vi, yielding compound 6 in 81% yield, p. 8104). Due to the reactivity of sterol side chain hydroxyl groups as compared to, for example, hydroxyl groups at C3 or C7, a result of steric effects, inductive effects, and other factors, the C24 hydroxyl protecting group of Moriarty et al. remains in place for most of the synthesis (twelve steps) before deprotection (step v, yielding compound 16, pp. 8104-5), recited as step (b) in claims 7-24. Further, Moriarty et al. teach the 7 α -hydroxy group as unprotected for most of the synthesis following its introduction (nine steps) before a protecting group is added after deprotection of the C21 hydroxyl group. Thus, Moriarty et al. teach what Nakazawa does not: protecting the side chain hydroxyl group, followed by reduction of carbon-carbon double bonds, and then deprotection, while leaving the 7 α -hydroxy group unprotected.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to synthesize (20S)-7 α ,21-dihydroxy-20-methyl-5 α -pregna-3-one using the same method and reagents taught by Nakazawa et al. but with the two steps reversed as taught by Moriarty et al., because, as recognized by MPEP 2144.04, selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results (*In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946)). Furthermore, a person of ordinary skill in the art would reasonably have expected to be successful because Moriarty et al. shows that reversing the order does not adversely affect the overall squalamine synthesis using similar reactive side chain hydroxyl groups as those set forth by Nakazawa et al.

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 1-9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13, 15, 16, and 18 of copending Application No. 10/594,164. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

a. Claims 1, 2, and 5 are provisionally rejected over reference claim 13, as evidenced by US PG Pub. 2007/0197490, for the following reasons:

- formulae I and III, recited in examined claims 1, 2, and 5, are identical to formula II in reference claim 13;
- examined claims 1, 2, and 5 recite a method for *selectively reducing* formula II in mixture of formulae I & II without identifying their ratios or the reagents with which the reduction is to be carried out, which encompasses reference claim 13, drawn to *reacting* reference formula I with an alkali or alkaline earth metal in the

presence of a proton donor and amine and/or ammonia, commonly known reagents in the Birch reduction. The instant specification uses “selectively reduce” to mean reduction of a carbon-carbon double-bond, and not the carbonyl oxygen of the ketone (p. 14, lines 18-19); the lithium-ammonia Birch reduction recited in the reference claims accomplishes exactly this, and does so in a mixture of the ketone and the ene-one; and

- formula II recited in examined claims 1, 2, and 5, while not illustrated in reference claim 13, is necessarily formed as part of the process of reference claim 13, in which the C4-C5 double bond of the diene is reduced faster than that at C1-C2, giving a mixture of 1-ene-one and ketone that shifts to the ketone product as the reaction proceeds until the ene-one has been consumed, so that a mixture of compounds of examined formulae I and II is inherently produced by the process of reference claim 13, before being reduced to the saturated ketone (of examined formula III, and reference formula II).

In summary, examined claims 1, 2, and 5 recite a reactant (a mixture of formulae I and II) and products (formula III) which are identical to the reactants (formed as the reaction proceeds to completion) and products (reference formula II) of reference claim 13.

b. Claims 3 and 4 are provisionally rejected over reference claim 15 for the reasons given in paragraph 8(a) above; in addition, the tert-butyl-dimethylsilyl hydroxyl protecting species recited in reference claim 15 anticipates the genus recited in examined claim 3, and is identical to the species recited in examined claim 4.

c. Claims 6 and 7 are provisionally rejected over reference claim 16, as evidenced by US PG Pub. 2007/0197490, for the following reasons:

- formula VII recited in examined claims 6 and 7 is identical to formula IV in reference claim 16;
- formulae IV and VI recited in examined claims 6 and 7 are identical to formula III in reference claim 16, to include the scope of the variable groups R21 and R31;
- the two-step process recited in examined claims 6 and 7, which comprises
 - (i) selectively reducing a carbon-carbon double bond of formula V, and
 - (ii) eliminating the hydroxyl-protecting groups,

is substantively identical to the process recited in reference claim 16, which comprises

- (i) reacting formula I with an alkali or alkaline earth metal in the presence of a proton donor and and amine and/or ammonia so as to reduce its carbon-carbon double bonds to single bonds, and
 - (ii) eliminating the hydroxyl-protecting groups,
- to arrive at identical products (examined formula VII and reference formula IV.
- While reference claim 16 does not explicitly teach formula V, or a mixture of formulae IV and V, both are inherently formed during the alkali-ammonia reduction step of reference claim 16, in which reduction of the C4-C5 double bond of the diene (reference formula I) is proceeds faster than that of the C1-C2 double bond, resulting in a mixture of protected 1-ene-one (examined formula V) and protected ketone (examined formulae IV and VI) that shifts to the ketone

product as the reaction proceeds until the ene-one has been consumed, so that a mixture of compounds of examined formulae I and II is inherently produced by the process of reference claim 16, before being reduced to the saturated ketone (of examined formula III, and reference formula II).

In summary, examined claims 6 and 7 recite a reactant (a mixture of formulae IV and V); a process comprising a reduction step followed by a deprotection step; a protected first product (formula VI); and a deprotected second product (formula VII), which are identical to the reactant (a mixture of protected ketone and protected 1-ene-one corresponding to examined formulae IV and V, formed as the reaction proceeds); the process comprising a reduction step followed by a deprotection step; the protected first product (formula III); and the deprotected second product (formula IV) of reference claim 16.

d. Claims 8 and 9 are provisionally rejected over reference claim 18 for the reasons given in paragraph 8(c) above; in addition, the tert-butyl-dimethylsilyl hydroxyl protecting species recited in reference claim 18 anticipates the genus recited in examined claim 8, and is identical to the species recited in examined claim 9.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

11. Claims 1-9 are rejected.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARA E. CLARK whose telephone number is (571) 270-

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7672. The examiner can normally be reached on Mon - Thu, 7:30 am - 5:00 pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick J. Nolan can be reached on 571-272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SEC

/Patrick J. Nolan/
Supervisory Patent Examiner, Art Unit 4121